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10/588,564	08/04/2006	Dhiren N. Mistry	11336.1020USWO	8265
52835 7590 11/12/2008 HAMRE, SCHUMANN, MUELLER & LARSON, P.C. P.O. BOX 2902 MINNEAPOLIS, MN 55402-0902				
EXAMINER NOLAN, JASON MICHAEL				
ART UNIT		PAPER NUMBER		
1626				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/588,564

Applicant(s)

MISTRY ET AL.

Examiner

JASON NOLAN

Art Unit

1626

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 August 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SI/309)
Paper No(s)/Mail Date 12/13/2006
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

This Office Action is responsive to Applicant's Preliminary Amendment, filed 08/04/2006. Claims 1-47 are pending in the instant application; of which Claims 3, 4, 6, 8-12, 14, 17, 19, 21-23, & 26 are currently amended and Claims 33-47 are new.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on 12/13/2006 has been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Claim Objections

Claims 1, 4, 6, 8, 13, 14, 16-18, 26, 27, 35, 36, & 47 are objected to because of the following informalities:

Claims 1, 8, 13, 27, & 36 are objected to for not ending with a period.

Claims 1, 6, & 36 are objected to for having two consecutive commas in the text.

Claims 26 & 47 are objected to for having a period after step (ii).

Claims 24 & 26 are objected to for not having a space between words in "claim1".

Claims 27 & 29 are objected to for not having a space between words in "claim2".

Claims 9, 37, & 45 are objected to for not having "claim" in the phrase "as claimed in 1[or 2]" before the claim number.

Claim 12 is objected to for not having a comma between members in the list.

Claims 4, 14, 16-18, 27, 28, 30, 34, 41, & 43 are objected to for not being in proper alternative form. See MPEP 2172.05(h).

Claims 1-3 & 33 are objected to for the term "its". The use of possessive grammar is confusing. Specifically, the phrase "or its addition salts . . ." should be amended to a more common phrase, for instance: "or an addition salt thereof."

Claims 1 & 2 are objected to for the term "their". The use of possessive grammar is confusing. Specifically, the phrase "acid catalyst and their salts" should be amended to a more common phrase, for instance: "acid catalyst and salts thereof."

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 31, & 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims must, under modern claim practice, stand alone to define an invention, *Ex parte* Fressola, 27 USPQ 2d 1608 (1993). Claim 1 does not provide a structure formula II and Claims 31 & 32 recite, "such as herein described with particular reference to the examples," such that one must refer back to the specification to define the claimed invention.

Claims 5-8, 10, 13, 16, 23, 25, 27-29, 35, 36, 38, & 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention: the terms "preferably," "more preferably," "such as," and "and the like" render the claims indefinite because it is unclear whether the limitations following the phrase are part of the

invention and lead to confusion over the intended scope of the claim. See MPEP § 2173.05(d).

Claims 1-3, 8, & 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the phrase "in polar aprotic solvent or its mixture with organic solvent, capable of removing water azeotropically" may be interpreted in more than one way. It is unclear if the polar aprotic solvent is capable of removing water azeotropically; or if the organic solvent is capable of removing water azeotropically; or if the mixture of a polar aprotic solvent and organic solvent is capable of removing water azeotropically. Instead of describing the properties of the organic solvent it is suggested to list specific organic solvents and deleting the language "capable of removing water azeotropically."

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-47 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for the preparation of compounds and salts according to Formulae I & II, does not reasonably provide enablement solvates according to Formulae I & II. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

1) *The nature of the invention* – an improved process for the preparation of compounds, salts, and solvates according to Formulae I & II.

2) *The state of the prior art* – the occurrence of hydrated or solvated crystal forms is widespread but my no means universal among drug substances. Some classes of drugs substances form solvates and others do not. Byrn et al. Solid-State Chemistry of Drugs, 2d, Chapter 11 Hydrates and Solvates, 233-247, 233.

3) *The predictability or unpredictability of the art* – the formation of solvates is unpredictable. Byrn states on p. 234, "Because prediction of crystal structures is not yet generally possible, we must be content with examining the crystal structures of compounds *after the fact* in looking for explanations of why solvates do or do not form. On doing so, however, we are left with only vague impression..." (Emphasis added). Byrn et al. at 234.

4) *The amount of direction or guidance presented* – there are no examples demonstrating that the compounds according to Formulae I & II may form solvates, as indicated. The amount of guidance or direction to enable an invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. MPEP 2164.03 (quoting *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 24 (CCPA 1970). As identified *supra*, the formation of solvates is unpredictable. The direction or guidance present in Applicants' Specification does not direct to which solvents or conditions are required to form solvates of the compounds according to Formulae I & II. For instance, some of the solvents used to form solvates are nonhydrogen-bonding solvents and serve only in a space-occupying capacity. On the

other hand, some solvents are capable of hydrogen bonding, which can stabilize a crystal structure either by improving the packing or via intermolecular bonding. Byrn et al. at 234.

5) *The presence or absence of working examples* - there are no examples demonstrating that the compounds according to Formulae I & II may form solvates, as indicated.

6) *The breadth of the claims* – the breadth of the claims is incommensurate in scope with the disclosure. Specifically, solvates are outside of the breadth of the disclosure.

7) *The quantity of experimentation necessary* – the amount of experimentation includes the adequate selection of the proper solvent and the crystallization technique. As pointed out in Byrn et al. in Table 11.3 there are numerous solvents to choose from. One of skill in the art only has a “vague impression” on explanations of why solvates do or do not form. Thus, because of the unpredictability of the art the process is trial and error.

8) *The level of skill in the art* - the level of the skill in the pharmaceutical arts, specifically in formation of solvates, is high.

Conclusion - Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. This rejection may be overcome by deleting the word “solvates” in all claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,886,812 (IDS) in view of US 7,285,669 and Schneider et al. (IDS).

1. *Determining the scope and contents of the prior art:* The instant steps (a)-(e) - the synthesis of formula (VIII) beginning with 4-aminocyclohexanol (formula III) and phthalic anhydride to produce formulae (IV), (V), (VI), and (VII) in succession are known in the prior art. See US 4,886,812, which teaches said synthesis in Example 2: cols. 14 & 15. The instant steps (f) & (g) - the resolution of formula (VIII) to formula (II) and alkylation/reduction to obtain formula (I) are known in the prior art. See Schneider et al. J. Med. Chem. 1987, 30(3), which teaches the resolution of racemic 4,5,6,7-tetrahydrobenzothiazole (8) with (L)-tartaric acid and subsequent conversion of (8) to (5), [formula (II) to formula (I)]. See Scheme I, p.495; experimental details on pp. 497-8. The instant step (d) - the process of brominating and subsequently converting with thiourea formula (V) to afford formula (VII) without isolation or in situ is known in the prior art. See US 7,285,669, cols. 3 & 4, Example 1 and Claims 1 & 2. Thus, the invention in Claims 1 & 2 is a combination of processes known in the prior art.

2. *Ascertaining the differences between the prior art and the claims at issue:* there is no difference between the steps utilized in the instant application and the teachings of the prior art. Applicant's point out the following deficiencies of the prior art: (i) yield, (ii) bromination with hydrobromic acid (Claims 11 & 39 outline the same bromination procedure as the prior art: i.e. Schneider et al.), and (iii) & (iv) the purification of certain intermediates by column chromatography (US 7,285,669 teaches that isolation & purification are not required for certain intermediates). See pp. 3 & 4 of the instant specification. Thus, the difference between the instant application and the prior art is the selection of solvents, acid catalysts, reaction times, reaction

temperatures, bases, and some reagents within the synthetic procedure. In determining the differences between the prior art and the claims, the question under 35 USC 103 is not whether the differences themselves would have been obvious, but whether the claim invention as a whole would have been obvious. See MPEP 2104.02. As pointed out, the prior art teaches the use of BR2 in bromination, as well as that some key intermediates need not be isolated and purified before subsequent use. Therefore, the difference in yields remains.

3. *Resolving the level of ordinary skill in the pertinent:* the level of the skill in the pharmaceutical arts is high.

4. *Considering objective evidence present in the application indicating obviousness or nonobviousness:* Examples 1-9 describe the experimental processes utilized in the synthesis as described in the instant Claims 1-47. The yields per each synthetic step range from 63-99%. The yields per each synthetic step in the '812 Patent range from 26-87%, wherein the step having the 26% yield is equivalent to the instant step (d). Step (d) is shown in the instant specification as Example-5, wherein the product was isolated via recrystallization. Since the reaction conditions between the instant application and the prior art are nearly identical, the low yield in the prior art was probably due to the purification by column chromatography. Although the difference in yield is 62%, it is not necessarily unexpected in the art for basic (nitrogen containing) compounds to decompose during purification via column chromatography due to the acidic nature of silica gel. Thus, one skilled in the art would be motivated to utilize the

processes taught in the prior art, but vary the style of purification to arrive at the instant claimed process with improved yields with a reasonable expectation of success.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jason M. Nolan whose telephone number is (571) 272-4356 and e-mail is Jason.Nolan@uspto.gov. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph M^cKane can be reached on (571) 272-0699. The USPTO fax number for applications is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system, (either Private PAIR or Public PAIR). Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. For questions on Private PAIR system, contact the Electronic Business Center at (866) 217-9197.

/Jason M. Nolan/

Examiner, Art Unit 1626

/Kamal A Saeed/

Primary Examiner, Art Unit 1626